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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,806	07/17/2003	Sylvia Daunert	50229-378	8451

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EXAMINER	
GRUN, JAMES LESLIE	
ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/620,806	DAUNERT ET AL.	
	Examiner	Art Unit	
	JAMES L. GRUN	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2008 and 23 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,8,9,11-14,19,20 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *22* is/are allowed.

6)☒ Claim(s) *1,2,4,5,8,9,11-14,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

The amendment filed 27 June 2008 is acknowledged and has been entered.

Claim 22 is currently allowable. The restriction requirement among inventions I-IV, as set forth in the Office action mailed on 20 June 2006, has been reconsidered in view of the allowability of claims to the elected invention pursuant to MPEP § 821.04(a). **The restriction requirement is hereby withdrawn as to any claim that requires all the limitations of an allowable claim.** Claim 18, which appeared to require all the limitations of an allowable claim, previously withdrawn from consideration as a result of the restriction requirement, was canceled by applicant in the reply filed on 27 June 2008. The canceled, nonelected claim(s) may be reinstated by applicant if submitted in a timely filed amendment in reply to this action. Upon entry of the amendment, such amended claim(s) will be examined for patentability under 37 CFR 1.104.

In view of the withdrawal of the restriction requirement as set forth above, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Claims 1, 2, 4, 5, 8, 9, 11-14, 19, and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant teaches a method using reagents comprising antibodies specific for 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$), a covalent conjugate of aequorin, preferably an aequorin mutant having a single cysteine residue, with 6-keto-$PGF_{1\alpha}$, and solid phase immobilized anti-immunoglobulin antibodies (see e.g. pages 13 or 15) for determination of 6-keto-$PGF_{1\alpha}$, a stable degradation product of prostacyclin (prostaglandin I_2), as an analyte indicative of prostacyclin. In the method, unlabeled 6-keto-$PGF_{1\alpha}$ analyte in a sample competes with the labeled conjugate of 6-keto-$PGF_{1\alpha}$ for binding to the anti-6-keto-$PGF_{1\alpha}$ antibodies, the antibody-bound conjugate or antibody-bound analyte is captured by the solid phase immobilized anti-immunoglobulin

antibodies, washed, and the amount of solid phase immobilized conjugate determined from measuring signal from the label is inversely proportional to the analyte amount in the sample.

The examiner would note that, in the method as described, the sample and unbound conjugate are washed from the solid phase thereby separating unbound sample components and unbound conjugate from bound conjugate and in no instance is the unbound conjugate separated from the sample. The bioluminescent signal of the bound conjugate, not the sample, is measured. Absent further written description and guidance from applicant one would not be assured of the ability to make and use the invention as instantly claimed wherein the unbound anti-6-keto-$PGF_{1\alpha}$ antibodies and the conjugate are removed from the sample or the light intensity of the sample is measured.

Moreover, although applicant teaches determinations of the levels of 6-keto-$PGF_{1\alpha}$ in the samples of some patients treated with prostacyclin, there would seem to be no correlation given, or easily discernible, for the relationship of 6-keto-$PGF_{1\alpha}$ to prostacyclin or prostaglandin level or dosage from the disclosure. The relevant level of 6-keto-$PGF_{1\alpha}$ to an "appropriate" dose of prostacyclin would seem unknown and unpredictable absent further experimentation to determine any correlations and absent further written description and guidance for what the dose is "appropriate." Is the level of 6-keto-$PGF_{1\alpha}$ dependent only upon the level of prostacyclin? Although levels of 6-keto-$PGF_{1\alpha}$ increase with increased dose of prostacyclin, what dose or level is "appropriate?" An indication that one is in possession of a method of determination of a metabolite does not necessarily place one in possession of all possible correlations with the metabolite. Such experimentation may be "obvious to try", but such an invitation to experiment

does not provide an indication that applicant had possession of the invention as claimed at the time the application was filed and does not provide an enabling disclosure.

Further, absent further written description and guidance from applicant one would not be assured of the ability to make and use the invention as instantly claimed wherein the effect of a therapeutic agent on the level of prostacyclin is determined with a single determination of 6-keto-$PGF_{1\alpha}$ in the sample. Some comparison with a standard or with a previous determination in the patient would seem to be required to determine an "effect" as claimed. Applicant is requested to direct the Examiner's attention to specific passages where support for these recited limitations can be found in the specification as filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, 5, 8, 9, 11-14, 19, and 20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 and claims dependent thereupon, the interrelationships of the components and steps of the method are not clear, e.g. there is no nexus between the incubating steps with reagents binding or conjugated to 6-keto-$PGF_{1\alpha}$, measuring light intensity of a plasma sample, and an amount or level of prostacyclin. In these claims, "the level" lacks antecedent basis.

In claim 5, "the concentration" lacks antecedent basis.

In claim 8 and claims dependent thereupon, the interrelationships of the components and steps of the method are not clear, e.g. there is no nexus between the incubating steps with

reagents binding or conjugated to 6-keto-$PGF_{1\alpha}$ and the measuring step. In these claims, "the amount of detected" lacks antecedent basis.

In claim 11, "The assay" lacks antecedent basis, --The method-- should be recited.

In claim 12, "the" concentration and assay lack antecedent basis.

In claim 13 and claims dependent thereupon, the interrelationships of the components and steps of the method are not clear, e.g.: there is no nexus between the incubating steps with reagents binding or conjugated to 6-keto-$PGF_{1\alpha}$, measuring light intensity of a plasma sample, and an amount or level of biomolecule; it is not clear for what the antibody is specific, 6-keto-$PGF_{1\alpha}$ or biomolecule; it is not clear for what the anti-immunoglobulin antibody is specific, immunoglobulin or biomolecule. In these claims, "the level" lacks antecedent basis. Claims 13 and 14 appear to claim subject matter indistinct from, and duplicative of, that claimed in claims 1 and 2.

Claim 19 depends from a cancelled claim. In this claim, "[t]he" biomolecule or biomolecule conjugate lacks antecedent basis.

In claim 20, the interrelationships of the components and steps of the method are not clear, e.g. there is no nexus between the incubating steps with reagents binding or conjugated to 6-keto-$PGF_{1\alpha}$, measuring light intensity of a plasma sample, and an amount or level of prostacyclin. In this claim, "the" effect and level lack antecedent basis.

Claim 22 is currently allowable.

Applicant's arguments filed 27 June 2008 have been fully considered but they are not deemed to be persuasive.

Notwithstanding applicant's assertions to the contrary, applicant's newly rejoined claims are not allowable and are rejected for the reasons set forth above.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Desai et al. (Anal. Chem. 74: 3892, August 2002) teach the invention essentially as disclosed using the cysteine-free mutant of aequorin.

Pradelles et al. (Anal. Chem. 57: 1170, 1985) teach a competitive immunoassay for determination of 6-keto-prostaglandin $F_{1\alpha}$ on microplates. The assay utilized antibodies specific for 6-keto-prostaglandin $F_{1\alpha}$, enzyme-labeled 6-keto-prostaglandin $F_{1\alpha}$, and immobilized anti-immunoglobulin antibodies. The reference teaches enzyme labels as an alternative to radiolabels. In contrast to the invention as instantly disclosed, the reference does not teach aequorin labels.

Any of Kosak (US 4,604,364), Stults (US 5,486,455), or Liotta et al. (US 5,942,407) teach aequorin as an alternative label to radiolabels or enzyme labels in immunoassays.

Lewis et al. (Bioconjugate Chem. 11: 65, 2000) teach a cysteine-free mutant of aequorin for use as a label in binding assays.

Lüke et al. (J. Immunol. Meth. 148: 217, 1992) teach labeling of prostaglandins with a biotin-avidin bridge for use in immunoassay.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 11 a.m. to 7 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/J. L. G./
James L. Grun, Ph.D.
Examiner, Art Unit 1641
September 17, 2008

/Long V Le/
Supervisory Patent Examiner, Art Unit 1641